

ELAB GLP Subcommittee Executive Summary Report Prepared Following the April 16, 1998 Meeting of ELAB

Background: As a result of several Office of Inspector General (OIG) reports critical of the oversight/management of the Environmental Protection Agency's (EPA) Good Laboratory Practice (GLP) compliance monitoring program, in early 1996 a number of initiatives were born to attempt to identify solutions to the perceived inadequacies, culminating in the formation of a GLP Subcommittee under the Environmental Laboratory Advisory Board (ELAB). This Subcommittee was charged with the following responsibilities:

- Characterize the GLP laboratory evaluation needs of the Office of Prevention, Pesticides and Toxic Substances (OPPTS) and the Office of Enforcement and Compliance Assurance (OECA).
- Evaluate feasible alternatives to National Environmental Laboratory Accreditation Program (NELAP) accreditation.
- Examine program implementation strategies for each option evaluated.
- Determine the benefits of GLP accreditation to EPA and others.
- Determine how potential actions would impact Organization for Economic Cooperation and Development (OECD) programs and commitments.

Options Developed: Utilizing a reference base of relevant documentation (refer to Attachment 1), a list of laboratory evaluation needs was developed with input from OPPTS and OECA representatives on the team (see Attachment 2). From this list of needs, a set of 35 options for implementing the EPA-OECA program was derived that attempted to address not only the self-identified deficiencies of the current program but also those issues raised in the 1991-1992 OIG reports as well as some international concerns. Because many of the original options were similar in design, the options were reduced to five broader categories. These were further reduced, pursuant to the directives of the ELAB, to the following three option categories:

Option 1, Use of Existing Programs and Procedures to Upgrade the Current Process: It is important to realize that this option is not an option for status quo as changes to streamline the current program are necessary. The existing EPA OECA GLP compliance monitoring program would be continued but initially be augmented by redefining the universe of the facilities to be inspected with the focus on sponsor facilities with study directors and primary/major data generators, and by development of a registration list which includes all facilities which participate in any aspect of the regulatory data generation process.

The existing EPA GLP Compliance Monitoring Program would be augmented by recognition of sponsors' current and ongoing GLP inspection programs. In the current program sponsors have full accountability for the quality and integrity of the data they submit to EPA, however, EPA retains full responsibility for all aspects of compliance monitoring. In this option EPA continues its inspection/audit program in generally the same manner, but by recognizing current value in existing sponsors' GLP inspections of contract facilities, the OECA targeting scheme from the list of 2000-plus facilities would be altered. Sponsors (registrants) would have a new responsibility to report to EPA each time they evaluated a contract facility, preferably in an established electronic format. This report would not include findings, but would provide an indication of the level of external auditing of small contract facilities. EPA would retain the option to inspect any test site, but would prioritize its schedule to focus on regular inspections of sponsors, testing facilities with study directors and facilities generating the majority of the GLP data. By establishing a data base of sponsors' GLP inspections, EPA would be able to track the number of sponsors' inspections at sub-contracted test sites. Using this information, EPA would schedule other inspections at remaining test sites that generate a relatively small amount of the data. By supplementing its inspection schedules with recognition of sponsor' activities, EPA would be much more effective in adequately scheduling inspections of testing facilities that generate the majority of the GLP data.

All facilities which perform FIFRA and TSCA GLP studies for submission to EPA would be required to register their facility with EPA OECA. Facility registration would involve an initial submission of information and documents to establish the basic profile for the facility. Documentation could possibly include: Description of size, organization, and capabilities of the facility; the organization, functions, and procedures of the Quality Assurance (QA) unit; general description of instruments and equipment used at the site, and the number and areas of expertise of staff. It might also include a current listing of standard operating procedures, resumes, CVs and training records of key personnel, floor plans of the facility, and a current master schedule. On a periodic schedule, facilities would be required to resubmit certain documents and information. The Agency or a designated third party contractor(s) would audit the submitted documents. Even though registration would not confer approval, facilities with corrected minor GLP deficiencies would be provisionally registered, while facilities with major GLP deficiencies would be targets for inspection. Possible periodic submission of the facility's master schedule would provide a means of monitoring work intended for submission to the Agency. This would allow OECA to prioritize its inspections and conduct in-life audit reviews of on-going studies. To remain on the registration list, a facility would need to continue to maintain GLP compliance verified at some point by an EPA facility inspection audit.

Option 2, Augment the Current Program with Additional Resources: This option is an expansion of Option 1 consisting of obtaining additional funds directed specifically to increase the resources of EPA to conduct compliance monitoring audit/inspections so that sites could be visited by the Agency on a more frequent basis (every 2-3 years is the current international expectation). Resources for the additional funding projected by this option would come from one or more of three proposed sources: A) Increase EPA funds directed to OECA, B) Increase FIFRA/TSCA registration fees with new funds earmarked for OECA to conduct GLP inspections, or C) Funds could be obtained from an EPA OECA directed "GLP Inspection" fee.

Option 3, Institute an Accreditation Program: A significant conclusion of the 1991-92 Inspector General Reports on the U.S. EPA GLP program was that the frequency of inspections was inadequate to ensure the quality and integrity of data submitted to the Agency. The recommendation given in those reports was to establish a 3rd Party, privately operated GLP Accreditation program to supplement and become integrated into the current system. The purpose of this recommendation was to increase the scope of facilities inspected, to ensure the frequency of inspections, to meet the international and national mandates of the program, to limit or reduce federal costs, and to bolster the U.S. EPA program in general. In 1994, the OECD issued a position paper on Laboratory Accreditation. In summary, the OECD concluded that a program based solely on ISO Guide 25 would be inadequate for regulators to evaluate data supplied to determine risk to health and the environment. The EPA ELAB GLP Subcommittee concluded that any accreditation program developed in the U.S. must therefore be based on EPA GLPs and recognize the OECD GLP Principles and supporting Guidance Documents. OECD has not objected to having non-government assessors conduct inspections as long as there is government oversight and authority and the GLP Principles are followed. Thus, it would appear that EPA could establish a third party accreditation program as long as EPA played an appropriate role in establishing and overseeing the program. This conclusion is consistent with programs already in place in a few European countries.

Option 3 would involve the development of a private third party accreditation program which would be sanctioned by EPA for the purposes of inspecting and accrediting laboratories to GLP standards. Enforcement responsibilities would remain with the EPA. The program would include registration of laboratories, on-site inspections of the test site facility, along with technical and quality programs. A certificate could be issued for successful completion of the GLP compliance inspection, which could address international concerns and broaden market acceptance of the laboratory and data. As the Accrediting Authority, the U.S. EPA OECA would establish a program to recognize third party accrediting organizations or bodies to provide laboratory accreditation to a GLP standard. Interested stakeholders, including third party accrediting bodies, sponsors, contract laboratories and others would help develop recommendations for the Program Description including: A) OECA's responsibility as

the Accrediting Authority, B) Criteria for approving third party accrediting bodies, and C) Criteria for qualifying and training assessors. Interested third party accrediting bodies would develop their GLP accreditation program based on these conditions. These programs would be reviewed by OECA who would sanction acceptable programs. Continued approval would depend on OECA's monitoring and periodic re-approval of the accrediting program. Accepted accrediting bodies could publicize their approval and existing GLP accrediting program, and begin to accept applications and complete the accreditation process as described. A detailed description of the strengths and weaknesses of this option are outlined in Attachment 2.

Position Relative to NELAP: After considerable discussion concerning the inclusion of the FIFRA/TSCA GLP Programs in NELAP, the ELAB GLP Subcommittee members and the organizations they represent are overwhelmingly in opposition to the proposal of including the FIFRA/TSCA GLP Programs in the NELAP. The key issues that have unified the Subcommittee against this proposal include:

- The current voluntary state operated focus of NELAP vs. federally mandated GLP programs.
- NELAP accreditation based on ISO Guide 25 is an inadequate standard for GLP compliance monitoring.
- NELAP accreditation directed primarily toward environmental monitoring vs. FIFRA/TSCA focus on toxicology, analytical, efficacy, and field research laboratories.
- Standardized NELAP environmental monitoring programs based on a few well established analytical methods vs. FIFRA/TSCA GLP data generation programs for new product registrations based on several thousand specifically focused independent methods.
- The ELAB GLP Subcommittee sees a clear distinction between an independent 3rd party accreditation program and NELAP accreditation. Should EPA adopt an accreditation program within NELAP, the ELAB GLP Subcommittee believes that the implementation and long term management of the program would be much more difficult than an independent 3rd party accreditation program based solely on GLP and focused on FIFRA/TSCA regulations.
- Failure of NELAP to include the GLP regulated community in the initial Federal Advisory Committee and in drafting of NELAP standards prior to 1995.

Similar concerns have been expressed to the Assistant Administrators of OPPTS and OECA by the Association of American Pesticide Control Officials (AAPCO) who stated in an October 1997 letter that "...This concern is seriously compounded by the extraordinarily poor fit of the current NELAC standards to the state pesticide laboratories" (letter from Scott (AAPCO Pres.) to Goldman and Herman). In the State-FIFRA Issues Research and Evaluation Group (SFIREG WC/PD-M) meeting minutes of October 27-28, 1997, it was noted that "... Everyone concerned, including OPP management, is agreed that state pesticide labs are different from other labs, and therefore their standards should be different..."

Detailed descriptions of the issues and concerns of including FIFRA/TSCA GLP programs in NELAP are provided in Attachments 2 and 3 to this document.

Interagency Issues Concerning Laboratory Accreditation: The FDA has issued a position statement indicating they will not adopt an accreditation program, but will continue the GLP program currently in place for the registration of pharmaceuticals and other non-appliance health products. The FDA has concluded that a program of regular laboratory inspections and data audits, conducted by FDA personnel, was the most cost effective and efficient means to ensure the quality and integrity of data submitted to the FDA. It was also concluded by FDA to be the least burdensome to industry and most efficient for FDA oversight. There are currently no plans by the FDA to adopt an accreditation approach to regulate GLP laboratories. The FDA has concluded that the current program of internal QA and FDA inspections and data audits provides the necessary level of data quality and integrity with minimal outlay of resources (refer to Attachment 2).

International Issues Pertaining to US-EPA and the OECD-GLP Programs: The development of a United States GLP standard by the FDA in the late 1970's prompted interest in GLP on the part of other OECD Member countries in order to ensure continued acceptance of their data in the large U.S. market. OECD's involvement flowed logically from a principle purpose of all of its programs--- the avoidance of non-tariff trade barriers between OECD Member countries as a consequence of national regulatory programs. In general, the OECD Member

countries with national GLP programs have adopted the OECD Principles of GLP as the basic standard, as required by the 1981 Council Act. This is especially true for the 15 member states of the European Union, (whose standard is the OECD Principles verbatim), Japan (MHW, MAFF, MITI), the United States (FDA and EPA), and Switzerland. In general, there is a very high degree of harmonization amongst these countries.

Equally relevant to analyzing the impact and conditions of a US-GLP accreditation program is the evaluation of existing bilateral agreements and MOUs between the U.S. and OECD Member countries. These agreements reiterate provisions for meeting the Mutual Acceptance of Data Decision and goals, including promotion of data acceptance and reciprocity amongst participating countries, and continued cooperative relationship between countries. Requirements can be summarized into four general conditions: 1) Adherence to standards of GLP based on national GLP programs and the OECD Council Recommendations and Decisions; 2) Mutually consistent national programs, including periodic (approximately every two years) inspections by trained government inspectors, (or government sanctioned programs); 3) National compliance procedures, including notifying laboratories of observed deficiencies and requirements for corrective action; and 4) Periodically, providing the signatories with names and addresses of non-clinical health and environmental safety laboratories operating within the country and the dates of government or government sanctioned inspections, and current GLP compliance status.

None of these requirements either negate or promote the concept of developing a US-GLP Laboratory accreditation program. Critical, however, to evaluating the impact of accreditation on the US-EPA GLP program is the preamble to the document entitled "Revised Guide for Compliance Monitoring Procedures for Good Laboratory Practices." The preamble states that "Member countries will adopt GLP Principles and establish compliance monitoring procedures according to national legal and administrative practices..."

Cost/Benefit Analysis of Current Programs to Industry and Proposed Options: In an effort to determine the impact of GLPs on the cost of research, and to break out the cost of QA, a survey was developed and distributed to the EPA GLP community. From the results of this survey, it is clear that the current direct and indirect cost to industry for GLP QA programs exceed \$30 million annually. This number becomes particularly significant when it is realized that the OIG Reports issued between 1991 and 1992 did not give any consideration/credit for the impact that EPA regulated industry QA programs have on data quality, or frequency of internal inspections. The FIFRA and TSCA testing industry GLP QA program effort must be considered in whatever final decision is reached in the current oversight/monitoring debate if an acceptable cost effective revision is to be successfully implemented.

DISCUSSION AND RECOMMENDATIONS: In summary, the Subcommittee has developed three primary options for consideration by ELAB, as follows: 1) Implement adjustments to the existing program and procedures to upgrade the current compliance monitoring program, 2) Augment the current program with additional resources, 3) Utilize a 3rd party accreditation program to address frequency of inspection expectations. The need for intra-agency, interagency, and international harmonization as well as the impact of potential EPA action on these needs was also evaluated and concluded to play an integral role in any decision. The cost of the current EPA-GLP programs (including the stakeholders' QA oversight efforts) was also found to be significant and undervalued by much of the regulatory oversight community (especially international regulators).

The three final options proposed by the Subcommittee will vary in cost and implementation complexity, including their ability to address the various needs expressed in this report. Option 1 will allow the Agency to upgrade the existing GLP compliance monitoring program with minimal resource drain and added cost. It is expected that additional resources (both manpower and capital) will be required by OECA in order to satisfy the more complex concerns, including those of the international community and the OIG comments on frequency of EPA GLP compliance monitoring inspections. Options 2 and 3 provide additional ways to meet the longer-term compliance monitoring needs of the Agency. While it is clear that more resources should be made available to EPA's GLP monitoring and compliance program if all of the needs are to be met, the cost of adding these new resources must

be balanced with the cost of the current program. Any new processes must be value adding and cost effective for the entire industry (regulators and regulated community) if these processes are to be successfully implemented.

The interagency and international efforts to harmonize GLP programs and standards must also be weighted heavily in any decision to change the current program. Specifically, since these harmonization initiatives are likely to impact to some degree the options identified in this report (particularly the larger, more comprehensive options 2 and 3), and since the OECD revision efforts are fairly close to being realized, it is recommended that EPA decisions covering Options 2 and 3 be deferred until the new OECD GLP Principles are published and the harmonization activities are concluded.

In conclusion, the ELAB GLP Subcommittee offers the following set of recommendations:

1. Totally disengage the GLP issue and FIFRA/TSCA programs from NELAP activity and timeline. There are too many potential problems with integrating these programs into the NELAP proposal.
2. Focus immediately on implementing Option 1. Should this modification in concert with harmonization efforts with the OECD GLP Principles still not address the perceived deficiencies of the OECA compliance monitoring program, thereafter, consider on a longer-term scale, the value to be added by implementing other options identified in this report.
3. Utilize the rule-making process to amend the US FIFRA/TSCA GLP standards to meet EPA needs and the newly revised OECD Principles of GLP for alignment with the many international harmonization efforts underway at the current time.
4. Utilize the rule-making process to include the entire GLP regulated community in the review and comment on possible solutions to ensure that each facet of the new program is cost effective, value adding, and that redundancy is minimized.

Attachments:

1. Reference Documents.
2. Interim Report to the ELAB, February, 1997
3. Annual Meeting Report to the ELAB, July, 1997.